REMARKS

Applicants submit the following remarks in response to the Office Action dated July 8, 2009. Reconsideration of the application is respectfully requested.

Applicants' amendment of certain rejected claims is not to be construed as an admission that the Examiner's rejections were proper. The Applicants continue to believe that the rejected claims are described in and enabled by the specification, and are not anticipated by nor obvious in view of the cited references, as previously argued. The rejected claims have been amended for the sole purpose of advancing the case to allowance. The Applicants reserve the right to file a continuing application to continue the prosecution of the rejected claims.

Sequence Requirement Compliance

Applicants have attached herewith the requested replacement Sequence Listing. Applicants submit that no new matter has been added with this replacement.

Objection to the Figures

Applicants have attached herewith the requested replacement sheet (5/5) for FIG. 3A, FIG. 3B, FIG. 3C AND FIG. 3D to present the indicated amino acid sequences using one letter symbols with upper case letters. Applicants submit that no new matter has been added with this replacement.

Objection to the Claims

Applicants have amended claims 1, 4, 5 and 6 to address the objections of the Examiner.

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Rejections under § 112, 2nd paragraph

Claims 1 and 4-6 have again been rejected as indefinite in being unclear as to the meaning of the phrases "therapeutically active portion" or "active portion." The referenced claims have been amended as indicated above to recite that the indicated polypeptides are "active in inhibiting cell growth or proliferation and [. . . do] not have lysyl oxidase catalytic activity," as suggested by the Examiner. Support for these amendments can be found in the specification as filed at least at p. 1, lines 23-25, in combination with p. 3, lines 2-9, and p. 9, lines 8-11 and 12-13. Therefore, Applicants submit that no new matter has been added. Applicants further submit that given the support indicated above, the indicated claim amendments merely make explicit that which Applicants submit was implicit before as to the meaning of the indicated phrases and that the scope of claims 1 and 4-6 has not changed with these amendments.

In addition, Applicants have further amended claim 6 as required by the Examiner to make explicit that fragment L_2 ***IS*** a fragment of L_1 and not a separate fragment of the lysyl oxidase pro-peptide, which meaning Applicants believe was inherent before in the remaining wording of claim 6. Applicants submit that the scope of claim 6 and the claims dependent thereon has not changed with these amendments.

Applicants submit that all rejections under § 112, 2nd paragraph have been overcome.

Rejections under § 112, 1st paragraph

Claims 1-5 have been rejected for lack of written description and enablement support. Applicants submit that these two separate requirements have been improperly lumped together by the Examiner

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and that the Examiner has made excessive use of boilerplate rejections without sufficient attention to the specific subject matter of this application.

As described in both the Background section of the application and in Li et al., e.g., at p. 11, line 2 – p. 13, line 16, both lysyl oxidase and its proenzyme form are very well characterized, having been extensively studied in a number of species. Furthermore, it is well within the capability of those of ordinary skill in the art to isolate homologues of both lysyl oxidase and its proenzyme form for any other species desired. Thus, numerous additional variants of the lysyl oxidase pro-peptide, certainly sufficient numbers for a recognized genus, are easily accessible as well to those of ordinary skill, being merely the difference between a given lysyl oxidase and its proenzyme form.

As to whether Applicants are entitled to dependent claims that recite that the polypeptide of the claimed composition has the amino acid sequence of certain recited SEQ ID NOs or "conservative substitutions thereof," Applicants submit that to identify the reasonable "conservative" substitutions of a specific amino acid at a specific site in one of the identified sequences is well within the capabilities of those of ordinary skill in the art. For example, the accompanying article summary (French et al., What is a Conservative Substitution? *Journal of Molecular Evolution*. **19**(2):171-175, 1983) states:

> It is commonly recognized that many evolutionary changes of amino acid sequence in proteins are conservative: a substitution of one amino acid residue for another has a far greater chance of being accepted if the two residues are similar in properties. Here we investigate what properties are most important in determining the similarity of two amino acids, from the evolutionary

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> point of view. Our results confirm earlier observations that the hydrophobicity and the molecular bulk of the side chain tend to be conserved. More importantly they also show that evolutionary pressures favour the conservation of secondary structure.

Applicants submit that all three of these properties can be determined by inspection for a given candidate amino acid substitution for the pro-peptide of this well characterized enzyme and that what ***IS*** a "conservative substitution" for a specific amino acid, if any, is easily determined by those of ordinary skill in the art.

Thus, Applicants submit that all of the rejections under § 112 have been overcome.

Rejections under § 102(b)

Claims 1-3 continue to be rejected as anticipated by Li et al. (WO/0185157) ("Li"), the Examiner saying that this reference teaches "a therapeutic composition comprising a lysyl oxidase polypeptide without catalytic activity for the treatment of cancer/tumors." The Examiner cites to p. 10, lines 25-33 and p. 13, lines 25-28 of Li. Applicants submit that when the disclosure of Li is examined in more detail, it can be seen that the statements cited by the Examiner are directly contradicted by other statements in numerous places in the Li application, including the results of all of the experiments described in the Examples, and, thus, these cited statements were merely gratuitous on the part of the authors, contradicting their own experimental evidence. Consequently, the specific statements of Li that were cited by the Examiner would not have been accepted as believable by those of ordinary skill in the art at the time of the filing of

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the instant application, given all of the evidence to the contrary in the document. In particular, in relation to Applicants' invention, ***all examples provided by Li present results that depend directly on lysyl oxidase catalytic activity for their effects, in sharp contrast to the instant claims that unambiguously exclude lysyl oxidase catalytic activity.***

Therefore, Li cannot anticipate Applicants' claims 1-3. For example, starting in the Brief Summary of the Invention, at p. 4, lines 3-5, the Li specification states: "Administered in a pharmaceutically acceptable inert carrier substance, the inhibitor ***oxidizes*** cell growth factors ***at lysine residues.***" This same mechanism of action is further recited in the summary at p. 4, lines 16-18; p. 4, lines 25-29; and p. 6, lines 14-20. All of these cites are describing the ***normal catalytic activity of lysyl oxidase (LO)***, which is to ***oxidize specific lysine residues***, as pointed out in Li at p. 11, lines 3-5.

The rest of the paragraph on p. 11 that starts at line 3 describes a number of specific proteins that the prior art had recognized as being substrates for LO. ***All that is contributed by Li*** is a recognition that ***additional substrates of LO exist*** and that by acting on these additional substrates using the same catalytic activity, i.e., ***oxidizing*** these additional substrates ***at specific lysine residues***, a new effect can be obtained. This point is spelled out in Li in summary form at p. 15, lines 8-25, and is supported by experimental results cited at least at p. 43, lines 15-27; p. 50, lines 18-31; p. 52, lines 3-8; p. 53, lines 9-15; and 55, lines 6-14, and by the conclusion given at p. 57, line 18 - p. 58, line 20, that it is the ***catalytic activity of LO*** that is responsible for this ***therapeutic*** effect.

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In all of this discussion, Li uses the terminology "LO," meaning "lysyl oxidase." Li does ***not*** mean the proenzyme form of lysyl oxidase. In fact the proenzyme is discussed only once – in the paragraph starting at p. 12, line 28 – in a discussion of the synthesis of LO, where it is stated:

> ***LO*** is synthesized by fibrogenic cells as a ***46 kDa [kDa] proenzyme***. Following signal peptide cleavage and N-glycosylation the resulting 50 kDa [kDa] proenzyme is secreted and then proteolytically cleaved to the ***31 ± 1 kD functional species*** in the extracellular space[, releasing the pro-peptide].
>
> (emphasis and additional wording added)

Although Li does use the terminology "fragments and/or derivatives of LO and/or its homologues, with or without catalytic activity" at p. 13 to describe the claimed inhibitors as pointed out by the Examiner, on the very next page of the specification (p. 14) there is a more believable statement about what ***Li means to teach***:

> The therapeutically effective portion refers to a compound or composition effective to depress, suppress or inhibit mitogenesis, angiogenesis, or the transactivation effects of Tat. Such therapeutic agents include purified naturally occuring LO, human recombinant LO and ***catalytically active*** fragments (peptides) of LO.
>
> (Li et al., p. 14, lines 1-6, emphasis added)

Finally, the Applicants' position as to the true teaching of Li is further reinforced by the language of independent claims 1-3 of Li as published in that the second "wherein" statement of each reads "wherein said inhibitor ***oxidizes*** said [growth factor / angiogenic factor / transactivator] ***at lysine residues***," emphasis

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added. In other words, Li claims ***only*** "inhibitors" ***having the catalytic activity of LO***.

As Li teaches that a ***catalytically active LO*** (or portion thereof) is required for the disclosed ***therapeutic activity***, the reference is ***necessarily*** teaching a "functional" species that ***does not contain the pro-peptide portion of the LO proenzyme*** as pointed out above, in direct contrast to the Applicants' claims in the instant application.

Therefore, Applicants submit that Li cannot anticipate Applicants' claimed invention, where the therapeutically active polypeptide in the claimed therapeutic composition ***is*** a portion of a lysyl oxidase pro-peptide ***and does not*** have lysyl oxidase catalytic activity. Thus, the rejection is overcome.

Nor would Li, whether or not it is combined with other references, make obvious the Applicants' instant claims. As summarized above, Li teaches that a therapeutically active polypeptide ***must*** have the catalytic activity of lysyl oxidase, whereas Applicants teach and claim a therapeutic composition ***having a different therapeutically active polypeptide*** with the directly opposite activity. Thus, Li could never lead one of ordinary skill to, and thereby make obvious, the Applicants' claimed therapeutic composition, which must ***not*** have lysyl oxidase catalytic activity.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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